Short-term in-vivo precision for assessment of hand bone density with Dual Energy X-ray Absorptiometry (DXA) and Digital X-ray Radiogrammetry (DXR)

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1.0 Abbreviations

BMC	Bone mineral content
BMD	Bone mineral density expressed as g/cm^2
BMI	Body mass index (kg/m^2)
CI	Confidence interval
CV	Coefficient of variation
DXA	Dual energy x-ray Absorptiometry
DXR	Digital X-ray Radiogrammetry
ROI	Region of interest
ROIs	Multiple regions of interest
SDD	Smallest detectable difference
SD	Standard deviation
QUS	Quantitative ultrasound
QCT	Quantitative CT
RA	Rheumatoid arthritis
Accuracy:	Defined as the coefficient of variation between the results of the measurement involved and that of a reference method.
Precision	Defined as the coefficient of variation for repeated measurements.
ACR:	American College of Rheumatology

2.0 **Abstract**

Background: Quantitative bone measures have been proposed as a new outcome measure and a prognostic indicator of future disease course in RA. Hand bone mass has been shown to be associated with fractures both in primary and secondary osteoporosis e.g. rheumatoid arthritis (RA). Further, hand bone mass is a potential outcome marker in RA associated with disease activity, physical function and bone damage. Dual energy x-ray Absorptiometry (DXA) is considered as the gold standard among quantitative bone measures. Digital X-ray radiogrammetry is a new promising method for assessment of cortical hand bone mass assessed on conventional hand radiographs
The precision of any method is crucial for assessment of differences between groups and for changes over time on both a group level but particularly of importance on the individual level.
Objectives: The objectives for this study were to assess the hand BMD in-vivo short term reproducibility for DXR and DXA. DXR in-vivo short term reproducibility was calculated for healthy individuals and RA patients separately. DXA in-vivo short term reproducibility was calculated using healthy individuals only.
The long term phantom precision for DXA and DXR was also examined.
Material and Methods:
Subjects: 28 healthy subjects (mean (SD) age 29.8 yrs (8.3), BMI 23.4 kg/m2 (1.9), males 17 (60.7%)) and 39 RA patients (mean (SD) age: 55.8 (11.9) years. Body weight: 69.4 (13.4) kg. Females: 79.5%. Mean grip strength: 29.8 (22.6) for left hand and 28.6 (19.0) for right hand (kPa). Disease duration: 16.0 (12.6) years) with various disease severities ranging from mild to disabling disease were recruited and included in the study.
BMD measurement methods: Group-I (healthy individuals) underwent hand BMD measurements using both DXA (measuring whole hand as region of interest (ROI)) and DXR (measuring cortical bone at 2nd, 3rd and 4th metacarp). Group-II (RA patients) underwent DXR BMD-measurements. For DXA hand BMD we used the Lunar Expert system (Madison, Wisconsin) and for DXR hand BMD we used the Digital X-ray radiogrammetry Pronosco X-posure SystemTM, version 2.0.0 (Sectra Pronosco A/S, Herlev, Denmark)
Statistical analysis: In-vivo short term precision for both DXA and DXR was calculated from duplicate hand measures for each of the two devices with repositioning of the hand in between each measure. For each device mean values for the left and right hand was used. The long term phantom precision was also calculated for both devices. Reproducibility was expressed as smallest detectable difference with 95% detection limits (SDD, according to Bland and Altman), percentage coefficient of variation (CV%), and percentage SDD (based on the formula: $2*\sqrt{2}*CV\%$).
Results: Long-term spine phantom CV was 0.80% for DXA and long-term CV based on daily measurements of one hand radiograph was 0.25% for DXR.
Group-1 (healthy individuals):
Mean (SD) BMD for both hands was 0.612 (0067) for DXR and 0.450 (0.054) for DXA. The DXR CV for mean both hands was 0, 28%. The DXA CV for mean both hands was 0,76%. SDD with 95% limits of agreement was ±0.0048 for DXR and ±0.0098 for DXA. Percentage SDD was calculated as 0.79% for DXR and 2.15% for DXA.
Group-II (RA Patients): Mean (SD) DXR-BMD for both hands was 0.510 (0.108).

The DXR CV for mean both hands was 0, 46%. SDD with 95% limits of agreement was ±0.0065 (mean both hands) and percentage SDD was calculated as 1.30%.
Conclusions: The primary result was a low short time in-vivo precision error for both DXA and DXR. Our findings shows that the DXR method measuring cortical hand bone mass density has superior short-term in-vivo precision and is capable to detect very small changes in hand cortical bone mass. Our data also demonstrate that mean values of both hands should be used to achieve the best precision and that precision is dependent on the BMD level of the examined individuals. Whether DXR is more sensitive than DXA to identify patients with bone loss will also depend on magnitude of bone loss at the measurement site assessed by the two devices in a studied population. Thus, theoretically a higher rate of bone loss assessed with DXA than DXR in a studied population could compensate for the poorer precision. Further studies are needed to examine hand bone loss in different populations.

3.0 Introduction

3.1 Background

Rheumatoid arthritis (RA) is a severe chronic remitting relapsing inflammatory rheumatic disease which affects approximately 0.5-1% of the adult Caucasian population (1, 2, 3). The disease is characterised by synovitis and joint destruction and is accompanied by increased morbidity, disability and mortality. Osteoporosis is one of the many systemic, non-articular manifestations of RA, and is a well known and common complication in RA (4). In RA bone damage is caused by both osteoporosis and joint erosions and substantial data support that the osteoclast cell plays a major role in the development of both bone damage features (Fig.1).

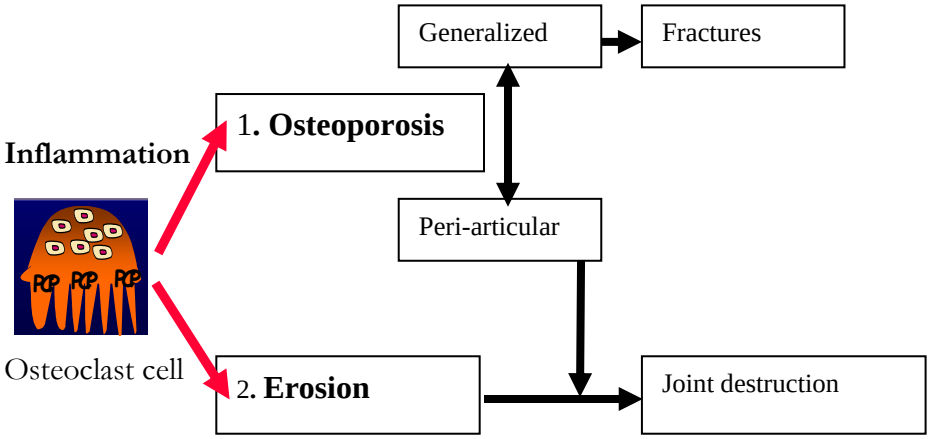

Fig. 1: Bone involvement in rheumatoid arthritis.
Glenn Haugeberg. Osteoporosis in Rheumatoid Arthrits.UIO 2003 (5)

Osteoporosis in RA occurs in two forms: periarticular osteopenia/osteoporosis adjacent to inflamed joints which is a characteristic of early disease, especially in the hands and feet, and generalized osteoporosis/osteopenia involving the axial and appendicular skeleton (6) associated with increased risk of fracture. Different underlying pathophysiologic mechanisms of the three bone manifestations in RA, the per-articular osteoporosis, the generalised osteoporosis and the erosions have been proposed (7). Bone erosions have been considered to be due to direct invasion by synovial pannus, peri-articular osteoporosis due to local production of large amounts of bone resorbing cytokines and generalised osteoporosis was considered multi-factorial with major contributions from disease activity, progressive loss of mobility and use of corticosteroids (7-9). Peri-articular osteoporosis and erosions are both X-ray findings that are included in the revised 1987 American College of Rheumatology (ACR) classification criteria for RA (6). The peri-articular bone loss is thought to develop more rapidly than generalised osteopenia in RA (10). The peri-articular local osteoporosis is a

typical early finding in radiographs in RA patients and occurres often before the typical erosions are visible on X-ray.
The term "early RA" is generally accepted as RA of less than 2 years duration (11). It is important with early assessment and treatment to achieve a good long-term outcome and limit irreversible joint damage. Most of the RA patients develop irreversible destructive joint damage early in the course of the disease, often within the first two years after disease onset (12). The most important time period for effective intervention is thought to be around the onset of the disease.
Clinical trials and cohort studies examining radiographic progression have clearly demonstrated a relation between inflammation (disease activity) and damage. In the early stage of RA it is well known that erosions on conventional radiographs may not be present. Conventional radiography used for scoring joint damage is considered to be the "gold standard" in the evaluation of the degree of bone damage caused by RA (13). The hand is the site of the earliest radiological changes in RA as it is directly affected by juxta-articular bone loss in the metacarpals. This may precede other characteristic radiological findings in RA, like erosions and joint space narrowing (13). The radiology technique is insensitive to bone changes in the early stages of RA and most of the patients with recent onset RA typically have normal hand radiographs even with clinical involvement of the small joints in the hands (12). Many RA patients will therefore present when radiographically detectable damage may not yet have occurred.

Measurement of BMD is widely used to diagnose osteoporosis, predict fracture risk and to evaluate response to therapeutic intervention. As osteoporosis (particularly peri-articular osteoporosis) is a direct consequence of the inflammatory disease process, bone mass measurements could in principle be an outcome marker of inflammation, of damage and could also be used as a marker of response to therapeutic intervention in RA patients. A rapid hand bone loss has been found both measured at the whole hand and measured peri-articularly (14). In clinical practice bone mass is quantitatively measurable by surrogate measurements using e.g. DXA (15), quantitative computer tomography (QCT) (16), DXR (17) and Quantitative ultrasound (QUS) (18). All methods are proven to have an acceptable precision (5). DXA has become the most widespread technique for determination of BMD and is considered as the "gold standard" among quantitative bone measures. DXR is a new promising method for assessment of cortical hand bone mass assessed on conventional hand radiographs. The method involves a complete automated procedure, without any guidance from the operator in finding the regions of interests (ROIs) of the 2^{nd}, 3^{rd} and 4^{th} metacarpal bones and provides an estimation of BMD from basic geometric measurements. The readings of radiographs and calculations of DXR-BMD can be performed centrally and reported back to the local physician. Retrospective analysis may also be performed.
Peripheral techniques, such as DXR, peripheral DXA or QUS make the bone densitometry service available to a greater proportion of the population, as it is relatively inexpensive The hand is easily accessible for measuring purposes and is for patients a highly acceptable site to measure. The DXR method works without an exposure standard, it is largely independent of the image capture conditions and the BMD values are, compared to DXA not dependent on body weight and body surface. On the other side, precision is found to be best with single (SF)-sided emulsion radiographic film (17, 19, 20).
The DXR method may be used to assess hand bone loss in RA, especially early RA. Jensen *et al.* (2004) concluded in a two year follow up study of patients with early RA and unclassified polyarthritis that DXR BMD decreased significantly only in patients with RA from month 6

and that the decrease was associated with the mean disease activity. They found that RA patients with active disease appeared to have a greater rate of bone loss as measured by DXR during the first six months compared with patients with inactive disease. No significant differences in the progression in the Larsen score (21) was found between the two groups. They suggested that DXR can give useful information and be a sensitive tool to measure bone loss early in the disease process of RA and that DXR has the potential to be a useful measure of destructive disease activity in patients with unclassified polyarthritis and early RA, concluding that DXR seems to be a better technique for detecting and monitoring peri-articular osteoporosis than DXA (12). Haugeberg *et al.* 2004 concluded that BMD measured by DXR in patients with RA may potentially be used as an indicator of joint damage (22). Jœrgensen *et al.* (2000) described that the performance of the DXR method seems to be at least equivalent with peripheral DXA (17). Böttcher *et al.* (2004) concluded that DXR-BMD measurements seem to be able to distinguish severity and progress of the disease in contrast to DXA measurements (at lumbar spine and total femur), and that the DXR method might be a possibility for reliable quantification of peri-articular demineralization induced by RA (23). It is also described that DXR from digitized images can predict at 1 year those patients with RA who will become erosive at 4 years (24). DXR might also be important in other clinical settings as Bouxsein *et al.* (2002) concluded that DXR-BMD performs as well as other peripheral BMD measurements for prediction of wrist, hip and vertebral fractures (25).

The objectives for this study are to assess hand BMD in-vivo short term reproducibility for DXR and DXA in healthy individuals and in-vivo short term reproducibility for DXR in RA patients with various disease severity and disease duration.
It is crucial to use measurement methods that are capable of detecting small, true significant changes and that the results are reproducible, especially over time. No bone densitometry technique is perfectly reproducible even when performed in accordance with the manufacturer's recommendations, and precision must be quantified at each center offering densitometry (26). The precision of any method is crucial for assessment of differences between groups and for changes over time on both a group level but particularly of importance on the individual level e.g. to monitor the course of suspected bone loss or follow the effect of therapy and to determine the minimum interval between follow-up measurements. Reproducibility is dependent of the capability of the device to reproduce the same result, and stable measurements over time.
Precision can be defined as the capability of the device to reproduce the same result under identical conditions. The precision error of the measurement tool is important in order to determine if a given change in BMD can be regarded as statistically significant (27)..
The minimal statistically significant change that can be determined by a method is directly dependent on the reproducibility (precision) of the method.
To verify if a given change in BMD (DXA, DXR) can be regarded as statistically significant, knowledge about the reproducibility (precision error) of the measurement device is necessary. With a confidence of 95%, a change in BMD of approximately $2\sqrt{2}$ times the precision error is required to be regarded statistically significant (27). Without a precision study the least significant change in bone density cannot be determined. Sensitivity to change for a method is calculated to determine how big the change has to be before one can conclude that a true change has taken place between two measurements in time on an individual basis. This limit is defined as the smallest detectable difference (SDD). A test is considered to be capable of detecting a difference of at least the magnitude of the limits of agreement.

The detection limit can be used to define a patient as true BMD loser, true gainer or as having a true stable BMD. "True BMD loser/gainer" in this context means that the BMD change exceeds the measurements error (SDD). The precision error is usually expressed as the coefficient of variation (CV), but the metric expression of smallest detectable difference (SDD) with 95% detection limits according to Bland and Altman 1986 (28)), may be preferable to the CV (29). Ravaud *et al.* (2000) suggested that precision errors should be based on SD (expressed in absolute units) rather than on CV (expressed in percentage) (30).

3.1 Study objectives

The objectives for this study were to assess hand BMD in-vivo short term reproducibility for DXR in healthy individuals and in patients with RA with various disease severity and disease duration, and to assess in-vivo short term reproducibility for hand bone density measured by DXA in healthy individuals.

4.0 Methods and materials

4.1 Study design

The study was conducted between June 2003 and December 2003 at the rheumatology outpatient clinic, Diakonhjemmet Hospital in Oslo. The X-rays were taken at Sentrum Roentgen, Oslo and at the radiology department, Sørlandet Hospital. The DXA scans were taken at the rheumatology outpatient clinic, Diakonhjemmet Hospital in Oslo. All scans and DXA-analysing were done by Anders Sandbu Strand. Statistical analysis was done with the help of Dr.med Glenn Haugeberg.
The in-vivo short-term precision for DXR was calculated from DXR-BMD measurements on duplicate hand radiographs.
The in-vivo short-term precision for DXA was calculated from duplicate DXA hand BMD measurements
The precision error was calculated separately for the dominant, non-dominant hand and for mean values of both hands. The precision error for the RA-group was calculated for the dominant hand and for mean values of both hands.
The long term phantom precision was calculated for both DXR and DXA based on daily measurements of standardised phantoms.

4.2 Subjects

In order to attain the study aims the study subjects were divided into two separate groups, Group-I (healthy individuals) and Group-II (RA patients).

Group-I:
31 healthy subjects were recruited among friends, relatives and colleagues. This group underwent hand BMD measurements using both DXA and DXR.
Subjects were excluded if they were using drugs or having diseases known to affect bone metabolism.
The participants filled out a questionnaire, and the subjects meeting the formal criteria were invited to participate. Individuals who turned out to have low bone mass were not secondarily excluded. Three participants were excluded because of missed X-ray appointments.

Group-II:
45 RA patients with various disease severities ranging from mild to disabling disease were recruited from the rheumatology department, Sørlandet Hospital. This group underwent DXR.
Six patients were excluded because of surgery metal involved in the DXR ROIs or that the radiographs did not pass the scanners quality control test.

None of the women included in the study were pregnant. None of the participants were under 18 years of age.

4.3 Hand BMD measurement methods

4.3.1 Digital X-ray Radiogrammetry.

The in-vivo short-term precision for DXR was calculated from DXR-BMD measurements on duplicate hand radiographs (AP view) taken within minutes according to a standardized protocol, performed with repositioning of the hands in between each X-ray. The hands were placed flat on the cassette with the palm side facing the X-ray cassette. The radiographs for Group-I were obtained at Sentrum roentgen clinic Oslo, using GE Telegem II X-ray equipment. (X-ray tube voltage: 55 kV, exposure dose: 6 mAs. Film/focus distance (FFD): 1 m). The film used was DF Fuji film with Agfa cassettes. All X-ray films were developed using an Agfa Curix Compact processor. Radiographs for Group-II were obtained at the radiology department at Sørlandet hospital, using Toshiba -DST 100A X-ray equipment (X-ray tube voltage: 52 kV, exposure dose: 5, 5 mAs, film focus distance: 1, 0 m, fine focus: 0, 6 mm). Film processor: Agfa - curix compact plus. The film used was ortho fine, Agfa.
Hand BMD was, after development of the radiographs, measured using DXR. The Pronosco X-posure software itself checked the quality of the scanned images and interrupted the examination in case of inadequate quality. Scanning and analysis of the image takes about 6 min per hand. Calibration and quality assurance testing of the scanners was performed in accordance with the manufacturer's standardized protocol. A phantom radiograph (50 kV, 6,

4 mAs, Fuji Film HR-L foil: Ca00 OG-2) was analyzed every day. Long-term phantom precision for DXR based on daily measurements of one hand radiograph is expressed as CV(%).

4.3.1.1 The DXR method and background:

The DXR method is implemented in the Pronosco X-posure SystemTM, V.2 RAD full edition version 2.0.0 (Sectra Pronosco A/S, Herlev, Denmark). DXR is a computerized version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin in 1960 (31). The technique measures the cortical thickness at the 2nd, 3rd and 4th metacarpal bone on hand X-rays (conventional or digitally acquired radiographs).

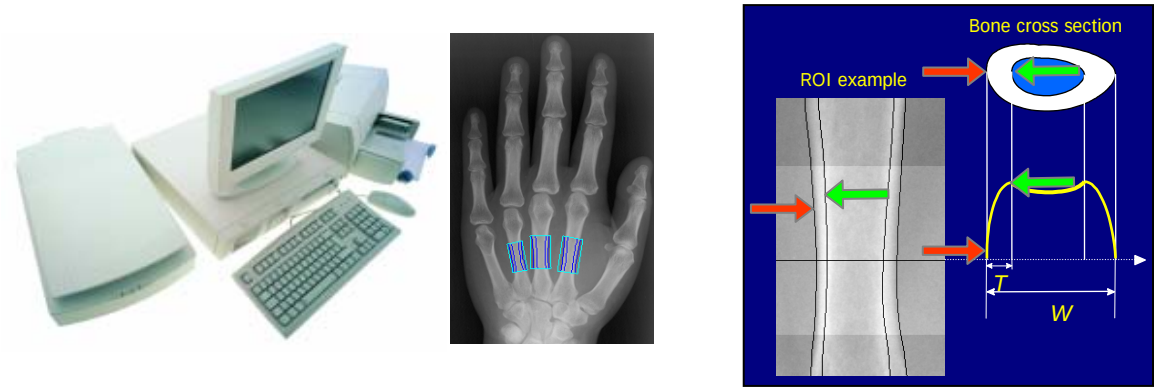

Fig. 2

Fig. 2: The illustrations are demonstrating the hardware needed for DXR, the ROIs in a hand radiograph and the basic DXR methodology.

The DXR method has been developed attempting to bridge the gap between radiogrammetry and densitometry from an assumed physical model of the bone. The DXR system combines radiogrammetry and texture analysis. This technique provides an estimation of BMD from basic geometric measurements, automatically conducted in a single radiograph of the hand. In contrast to DXA, radiogrammetry does not use the intensities of the image in a quantitative manner, but relies on geometric measurements. An exposure standard is therefore not needed. The method is largely independent of image capture conditions (32).The procedure is completely automated, as the program detects and analyses the three metacarpal bones without any guidance from the operator.

The Basic DXR Methodology (33):
The basic radiogrammetric methodology is an automated segmentation of a given diaphysis into cortical and medullar regions. The periosteal edge of a bone is defined as points with high curvature while the endosteal edge is defined as points with high intensity. This segmentation of the diaphysis enables the measurement of an average cortical thickness and an average width of the bone over a given region of interest (ROI) In each ROI the outer and inner edge of the cortex are determined.The cortical thickness and the bone width are calculated 118 times per centimeter in each ROI. The average cortical thickness and bone

width are determined for each metacarpal. Both cortices contribute to the calculation of the cortical thickness of the bone. From the cortical thickness T and the outer width W of a bone, a compound measurement named Bone Volume per Area (VPA) is derived. VPA is defined as the bone volume per projected area: VPA = Bone volume/Area. It is assumed that the general shape of the bone is constant, while the cortical thickness and width of the bone vary. To achieve the benefits of improved precision and accuracy enabled by computer processing power, the VPA analysis is applied to the three metacarpal bones and a combined VPA is calculated as a weighted average over these bones. The metacarpal ROIs are placed around the narrowest parts of the bone. The equal contribution provides reduction of the measurement noise.

The DXR method links VPA to BMD via the universal proportional relation between the mass m of a body and the volume V of the body: $m = \varrho \times V$. ϱ is, in this context the volumetric density of mineral matter in the bone. The mineral density respects partly the degree of mineralization and partly the presence of cavities not occupied by mineral matter. The mineral density has been found to be approximately constant when adjusting for porosities. The DXR method employs the fact that a good approximation to BMD may be obtained by multiplication of VPA by an appropriate constant, although there may be individual variation in the volumetric mineral density ϱ.

The DXR method involves a minor correction for porosities in cortical bone. Porosity is the fraction of the cortical volume, which is not occupied by compact bone. This correction is used to correct for over-estimation of BMD. Porosity for each of the involved bones in the ROIs is derived from the area percentage of local intensity minima (holes) found in the cortical part of the bone, relative to the entire cortical area. Intra-cortical porosity is influenced by age. The DXR BMD value is also corrected for striation which, together with porosity reflects the bone architecture, and mainly reflects the irregularity of the inner surface of the cortical bone. The presence of striation tends to slightly increase the measured cortical thickness. VPA is therefore gradually reduced by the system, via textural analysis if striation is present (17).

The software derives the DXR BMD (g/cm^2) = $c * (1 - P) * VPA$. (P is the estimated three-dimensional porosity and c is a scaling factor).

In a clinical setting, radiographs are acquired under the influence of a range of potentially varying capture conditions, which by their variation could affect the precision of the DXR BMD measurement. A study has assessed the capture induced variations in BMD-DXR, quantifying the measurement variation across different X-ray installations. They concluded that the magnitude of capture-induced variations corresponded to approximately 1% of the mean BMD-DXR value of young adult women (0.600 g/cm2) (33). It is also described that realistic deviations from a standard protocol for the capturing conditions did not influence the estimated BMD value and that successive measurements on the same patient may as well be performed at different X-ray installations since the main variation on the BMD assessment is due to variation of operators (34). Ward *et al.* (2003) found a significant, systematic difference between DXR-BMD measured from double (DF) - and single (SF) sided emulsion radiographic film, concluding that the precision is better with SF- than DF-radiographic film (20). The manufacturer's recommendations specify that best results are obtained by using Single-emulsion (SF) mammography film combinations for measurement of BMD using the X-Posure system. DF films are the most used film for general radiography in radiology departments. The manufacturer specifies that is important to use the same film type when reexamining a patient. The most appropriate DXR T-scores for detection of women with osteopaenia/ osteoporosis on DXA are described and it has been

concluded that T-scores from measurements on DF film should not be used, since the normative reference range provided by the manufacturer is based upon measurements made using SF film (20).
The BMD estimate generated by the DXR method has shown a high correlation to forearm DXA BMD (r=0 ·9) and correlation with BMD at the spine, total hip and femoral neck (33, 35, 36)

4.3.2 Dual energy X-ray absorptiometry. Lunar Expert (Madison, Wisconsin)

Fig. 3

Fig. 3: The illustrations demonstrate DXA equipment and the DXA ROI for hand BMD measurements.

The in-vivo short-term precision for DXA was calculated from duplicate hand measurements (dominant and non-dominant, defining the whole hand as ROI, done by dissecting between the carpal bones of the wrist and the radius and ulna and including all hand bones) using the Lunar Expert (Madison, Wisconsin). All procedures were in accordance with the manufacturer's standardized procedures for hand BMD measurements (Mode: 1mA fast. Field: length: 23 cm height: 14.4 cm. Exposure factor: time (sec): 18.9, voltage (kVp): 134.0, Current (mA): 1.0).
It is described that the total hand ROI is equivalent to smaller juxta-articular ROIs for monitoring change in DXA hand BMD in RA patients (37).
Between each capture, the hand was repositioned by having the subject remove the hand from the device until the next capture. The duplicate measurements were taken within minutes. Calibration and quality assurance testing of the scanners was performed daily. For long term quality assurance the machine was calibrated daily with an aluminum spine phantom supplied by Lunar. The phantom measurements showed stable results at the time of the study. Short-term in-vivo precision (CV) reproducibility for this Lunar Expert machine is previously reported to be 1.5 -2.2% (femoral neck, total hip, spine L2-4) and SDD (g/cm^2) 0.045, 0.037 and 0.084 for femoral neck, total hip and spine L2-4 respectively with a 95% CI (5).

4.3.2.1 The DXA method and background:

Bone densitometry was developed for diagnosis and treatment evaluation of osteoporosis. DXA is the most widely used modality for bone mineral density (BMD) measurement. It is considered as the "gold standard" among quantitative bone measures. DXA is widely used by physicians and is the gold standard used in most international clinical trials to calculate bone density.
It is a sensitive, reproducible, accurate and precise non-invasive tool with stable calibration and low radiation dose, to measure bone loss quantitatively (5).
The definitions of osteopenia and osteoporosis, as proposed by WHO (38), are based on results of DXA measurements as DXA provides an accurate and precise method of measuring BMD at the spine and hip. The method is based on the known differences in absorption of high energy and low energy X-rays by bone and soft tissue. The relative attenuation of two different energy levels can be used to subtract the soft tissue component making it possible to calculate the attenuation of the bone.
To measure BMD, bone is projected onto a plane, a certain region of interest (ROI) of the bone is identified and BMD is defined as the mineral mass of the bone projected onto this region, divided by the area of the region.
The software calculates BMD by measuring the bone mineral in a given ROI. BMD is measured in g/cm^2 and is derived using BMC divided by area. BMC is measured in grams (g) and area is measured in centimeters squared (cm^2). An exposure standard is needed.

4.4 Ethics

The study protocol was approved by the local ethical committee before the study was initiated. All participants were given written and oral information about the study. All of the participants had to give written consent to participate in the trial. The participants kept a copy of all given information. The study was carried out in accordance with the revised Helsinki Declaration (World Medical Association, 1996)

4.5 Statistical analysis

In this study reproducibility of the DXR and DXA methods is expressed as percentage coefficient of variation (CV%) (39), smallest detectable difference with 95% detection limits (SDD, according to Bland and Altman) (28), and percentage SDD (40).

Percentage coefficient of variation (CV%) is the most commonly presented measure for BMD variability. Coefficient of variation (CV) expressed as percentage is the percentage ratio of the standard deviation (SD) corrected for the mean of paired measurements (CV% = $\{\sqrt{(\sum D^2 / 2N)} / \text{mean}\} * 100$ (N = number of paired observations, D = the difference between the two measurements for each subject, Mean = Mean of all BMD measurements). The precision error was calculated separately for the dominant, non-dominant hand and for mean values of both hands separately for both DXR and DXA. The precision error for DXR RA patients was calculated separately for the dominant hand and for mean values of both hands.
The measurement error was calculated using Bland and Altman's 95% limits of agreement method. Precision expressed according to this method, also called SDD (smallest detectable difference (g/cm2)) gives an absolute and metric estimate of random measurement error and is independent of the BMD value (29). In this study, there are two observations for each subject and the standard deviation of the differences (SDdiff) estimates the within variability of the measurements (random measurement error). Most disagreements between measurements are expected to be between limits called "limits of agreement" defined as $d \pm z(1-\alpha/2)$SDdiff. d is the mean difference between the pairs of repeated measurements (The value d is an estimate of the mean systematic bias of measurement 1 to measurement 2. d is expected to be 0 because we do not assume a true change in BMD, as the duplicate X-rays and duplicate DXA measurements are taken whit in minutes) and $z(1-\alpha/2)$ is the 100(1-α/2)th percentile of the normal distribution. Defining α to be 5% (SDD 95% CI (g/cm²)), the limits of agreement are +1.96SDdiff and -1.96SDdiff. A test is considered to be capable of detecting a difference of at least the magnitude of the limits of agreement (29).
Percentage SDD is based on the formula: $2*\sqrt{2}*CV\%$. For two point measurements in time, a change (with 95% confidence) exceeding $2\sqrt{2}$ times the precision error of the technique is considered a significant change in an individual patient (40). Mean BMD was calculated as the mean of all BMD measurements for DXA and DXR separately.
The phantom long-term precision was calculated as CV% (SD/mean phantom BMD values for he measurement period * 100)

Statistical analysis was carried out using SPSS, version 11.0.0 (SPSS, Chicago, Illinois)

5.0 Results

5.1 Demographic and disease characteristics

Demographic and disease characteristics are displayed in table 1 for the healthy subjects (group-I) and the RA patients (group-II).

Table 1.Demographic data

	Group-I Healthy individuals	Group-II RA Patients
n	28	39
Age (years)	29.8 ± 8.3	55.8 ± 11.9
BMI (kg/m²)	23.4 ± 1.9	
Body weight		69.4 ± 13.4
Females (%)	39.3	79.5
Mean grip strength left hand (kPa)		29.8 ± 22.6
Mean grip strength right hand (kPa)		28.6 ± 19.0
Disease duration (years)		16.0 ± 12.6
Mean DXR-BMD (g/cm²)	0.612	0.510
SD DXR-BMD (g/cm²)	0.067	0.108
Mean DXA-BMD (g/cm²)	0.450	
SD DXA-BMD (g/cm2)	0.054	

The results are given as mean ± SD for the given demographic values.
Three participants were excluded from Group-I because of missed X-ray appointments.
Six patients were excluded from Group-II because the radiographs did not pass the DXR scanner quality control.

5.2 Long term phantom precision

The long-term spine phantom CV for DXA based on daily measurements of aluminum spine phantom supported by Lunar was 0.80%.
The long-term phantom CV for DXR based on daily measurements of one hand radiograph was 0.25%.

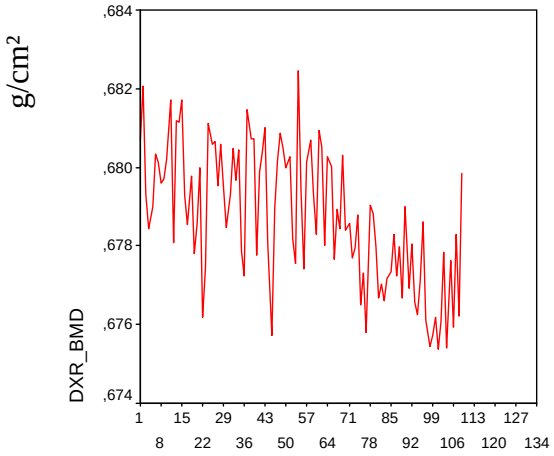

Fig.4

Fig.4. The illustration visualizes the DXR-BMD values from daily measurements of one hand radiograph in the period July 2001 to December 2003.

Fig.5.Curve estimation long term DXR-BMD values.

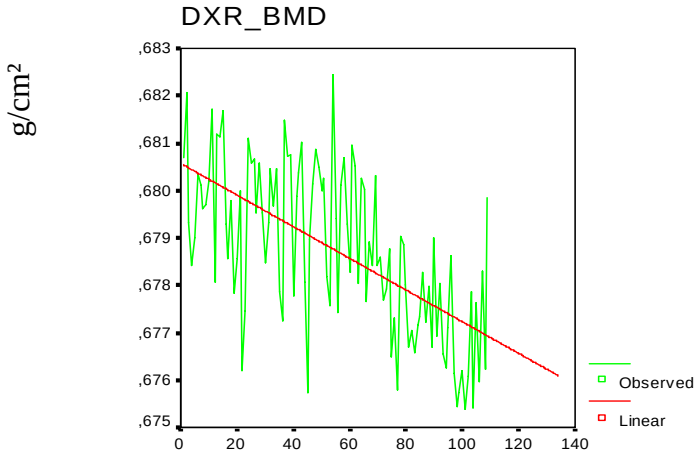

Fig.5

5.3 Reproducibility

Table 2 and 3 present the results of the different methods of calculating reproducibility for DXR and DXA.

Table 2. Reproducibility of DXR hand BMD measurements in 28 healthy subjects and 39 rheumatoid arthritis patients for the dominant hand and for the mean BMD values of both hands.

	DXR-hand BMD – Group-I Healthy individuals	
	Dominant hand	**Mean both hands**
Mean (SD) DXR BMD (g/cm^2)	0.623 (0.070)	0.612 (0.067)
Bland and Altman's methods		
Mean $_{difference}$ (95% CI) (systematic bias)	0.0003 (-0.0010, 0.0017)	-0.0001 (-0.00115, 0.0008)
SD $_{difference}$ (random measurement error)	0.0034	0.0025
SDD ~95% limits of agreement (assuming no systematic bias)	±0.0067	±0.0048
CV (%)	0.38%	0.28%
2√2CV (%)	1.07%	0.79%

	DXR-hand BMD – Group-II RA patients	
	Dominant hand	**Mean both hands**
Mean (SD) DXR BMD (g/cm^2)	0.513 (0.108)	0.510 (0.108)
Bland and Altman's methods		
Mean $_{difference}$ (95% CI) (systematic bias)	0.0008 (-0.0010, 0,0026)	0.0000 (-0.0010, 0.0010)
SD $_{difference}$ (random measurement error)	0.0057	0.0033
SDD ~95% limits of agreement (assuming no systematic bias)	± 0.0111	±0.0065
CV (%)	0.61%	0.46%
2√2CV (%)	2.21%	1.30%

Table 2 shows Mean BMD, Mean difference, SD difference, SDD, CV% and percentage SDD for DXR healthy individuals and RA patients, dominant and mean values of both hands.

Mean difference: mean of the difference between the first and the second hand BMD Measurement
SD difference: SD of the difference between the first and the second hand BMD measurement
SDD: smallest detectable difference (g/cm2)
CV: coefficient of variation
2√2CV: Percentage SDD

Table 2.

Table 3. Reproducibility of DXR and DXA hand BMD measurements for Group-I (healthy individuals)

	DXR-hand BMD Group-I Healthy Individuals		
	Non-dominant hand	Dominant hand	Mean both hands
Mean (SD) DXR BMD (g/cm^2)	0,602 (0,066)	0,623 (0,070)	0.612 (0.067)
Bland and Altman's methods			
Mean $_{difference}$ (95% CI) (systematic bias)	-0.0005 (-0.0019, 0.0008)	0.0003 (-0.0010, 0.0017)	-0.0001 (-0.00115, 0.0008)
SD $_{difference}$ (random measurement error)	0.0035	0.0034	0.0025
SDD ~95% limits of agreement (assuming no systematic bias)	±0.0069	±0.0067	±0.0048
CV (%)	0.41%	0.38%	0.28%
2√2CV (%)	1.16%	1.07%	0.79%

	DEXA-hand BMD Group-I Healthy individuals		
	Non-dominant hand	Dominant hand	Mean both hands
Mean (SD) DXA BMD (g/cm^2)	0,439 (0,056)	0,461(0,052)	0.450 (0.054)
Bland and Altman's methods			
Mean difference (95% CI) (systematic bias)	-0.0016 (-0.0044, 0.0011)	0.0006 (-0.0029, 0.0040)	-0.0005 (-0.0025, 0.0014)
SD difference (random measurement error)	0.0070	0.0088	0.0050
SDD ~95% limits of agreement (assuming no systematic bias)	±0.0137	±0.0173	±0.0098
CV (%)	1.13%	1.33%	0.76%
2√2CV (%)	3.20%	3.76%	2.15%

Table 3.

Table 3 shows Mean BMD, Mean difference, SD difference, SDD, CV% and percentage SDD for both DXA and DXR for dominant, non-dominant hand and mean values of both hands.

Mean difference: mean of the difference between the first and the second hand BMD Measurement
SD difference: SD of the difference between the first and the second hand BMD measurement
SDD: smallest detectable difference (g/cm2)
CV: coefficient of variation
2√2CV: Percentage SDD

6.0 Discussion

The DXR method is a new promising method in the assessment of cortical hand bone loss in RA, especially early RA. The method has the potential to be a useful measure of destructive disease activity and it seems to be a better technique for detecting and monitoring peri-articular osteoporosis than DXA. DXR may be able to distinguish severity and progress of the disease in contrast to DXA measurements and it has been described that DXR can predict at 1 year those patients with RA who will become erosive at 4 years.

When evaluating individual changes in BMD over time, knowledge about the reproducibility (precision error) of the measurement device is important in order to determine if a given change in BMD can be regarded as statistically significant

The primary result was a low precision error, both for DXA and DXR in healthy individuals and low DXR precision error for the RA patients. CV (%) DXR for mean both hands healthy individuals was 0, 28% and 0, 46% for RA patients. CV (%) DXA for mean both hands healthy individuals was 0, 76%. The Pronosco X-posure System will, at least in a relatively short-term period be able to detect a statistically significant change in BMD of approximately 0.79% in healthy individuals and approximately 1.30% in RA patients. For healthy individuals DXA will be, at least in a relatively short-term period be able to detect a statistically significant change in BMD of approximately 2.15%. Expressed as SDD, a DXR-BMD change should exceed 0.0048 g/cm^2 for mean both hands in healthy subjects and 0.0065 g/cm^2 for mean both hands in RA patients before it can be considered a significant change. This limit for DXA-BMD is found to be 0.0098 g/cm^2 in healthy subjects. It is concluded that the use of the SDD in the evaluation of an apparent BMD change gives a more conservative approach than the use of the CV at low BMD and that the SDD is a preferable measure for use in daily clinical practice as compared with the CV, because of its independence on BMD level and the expression in absolute units (29).

Our findings shows that the DXR method measuring cortical hand bone mass density has superior short-term in-vivo precision and is capable to detect smaller changes in hand bone mass than hand DXA. Comparison of DXR and DXA short-term precision is done thoroughly in other studies (17, 33). A problem with DXA is that the calibration may tend to drift over time and the method is also known to be sensitive to the thickness of soft tissue and physical movement of the equipment (17). The DXR method involves a complete automated procedure in finding the ROIs. These factors might all contribute to the lower DXR precision error observed.
When evaluating the clinical relevance of a short-term precision study, it is evident that it can not capture all the different sources of measurement noise that may influence measurements obtained over longer time intervals. Operator-dependent changes in the capture conditions and drift in the X-ray equipment may potentially increase the measurement noise. Nevertheless, the DXR method has been found to be largely independent of the image capture conditions. Precision is mainly found to be better with single (SF) - than double (DF-) - Sided emulsion radiographic film (20, 33, 34). The radiographs used in this study were obtained using DF-films. How this affects the observed short term precision is uncertain.

Our data demonstrate that mean values of both hands should be used to achieve the best precision and that precision is dependent on the BMD level of the examined individuals, as well as other factors that might influence the DXR precision in RA patients (e.g. positioning and deformations). It is described that a phantom and healthy young subjects are likely to show more favorable DXA variability than postmenopausal women possibly in part due to easier positioning for measurement, better DXA variability in children and that osteoarthritis in postmenopausal women might contribute to poorer DXA variability than found in the healthy young (29). How this affects the DXR variability is uncertain, but Jørgensen *et al.* 2000 reported DXR CV in a pre-menopausal group to be 0.68% and 0.61% in a postmenopausal group, concluding that the precision error for post-menopausal women is normally higher in DXA and that the DXR BMD for postmenopausal individuals can be expected to be better or at least as good as for younger, pre-menopausal individuals because of more precisely defined position of the intensity maximum in each subject (17). Rosholm *et al.* 2001 reported a DXR precision error of 0.60%, with the same precision among normal and osteoporotic subjects and that the decline in BMD-DXR with age became steeper than the decline in BMD-DXA, when adjusting for the inter-individual variation (33).
The DXA reproducibility for hand BMD measurements has been reported to be 1.1% (37).

Whether DXR is more sensitive than DXA to identify patients with bone loss will in addition depend on magnitude of bone loss at the measurement site, assessed by the two devices in a studied population. Thus, theoretically a higher rate of bone loss assessed with DXA than DXR in a studied population could compensate for the poorer precision. Further studies are needed to examine hand bone loss in different populations.

The study demonstrates that DXR has a low long-term phantom precision error (0,25%). The DXA long term phantom precision is also low (0,80%), and corresponds to results in other studies. The long time period used to obtain the phantom DXR-BMD measurements (2, 5 years) should capture most of the measurement noise that may influence measurements obtained over longer time intervals. The visual observed declining trend in the DXR long term phantom BMD-measurements is not investigated any further in this study. Factors that might contribute to this observation might be due to wear of the scanner hardware, the influence of light on the phantom radiograph, change of office or external factors that might influence the hardware (episode of power cut because of lightning). There is a need for additional research to confirm this observation and evaluation of the reasons.

7.0 References

(1) Hazes JM, Silman AJ. Review of UK data on the rheumatic diseases—2. Rheumatoid arthritis . *Br J Rheumatol* 1990;29:310-2

(2) Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States, *Arthritis Rheum* 1990;41:778-99

(3) Kvien TK, Glennås A, Knudsrød OG, Smedstad LM, Mowinckel P, Førre Ø. The prevalence and severity of rheumatoid arthritis in Oslo: Results from a county register and a population survey. *Scand J Rheumatol* 1986;29:494-500

(4) Deodhar AA, Woolf AD. Bone mass measurement and bone metabolisme in rheumatoid arthritis: a review. *Br J Rheumatol* 1996;35:309-22

(5) Glenn Haugeberg. Osteoporosis in Rheumatoid Arthritis. Faculty of medicine.University of Oslo. Dissertation for the Degree of Dr.med 2003.

(6) Arnett FC, Edworthy SM, Bloch DA, et al.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988, 31:315–324

(7) Sambrook P. The skeleton in rheumatoid arthritis: common mechanisms for bone erosions and osteoporosis? *J Rheumatol* 2000;27:2541-2

(8) Sambrook PN, Eisman JA, Champion GD, Yeates MG, Pocock NA, Eberl S. Determinants of axial bone loss in rheumatoid arthritis. Arthritis Rheum 1987,30:721-8

(9) Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet.* 1994 Jul 2;344(8914):23-7.

(10) Peel NF, Spittlehouse AJ, Bax DE, Eastell R.Bone mineral density of the hand in rheumatoid arthritis. *Arthritis Rheum.* 1994 Jul;**37**(7):983-91.

(11) Emery P, Symmons DP.What is early rheumatoid arthritis?: definition and diagnosis. *Baillieres Clin Rheumatol.* 1997 Feb;**11**(1):13-26.

(12) Jensen T, Klarlund M, Hansen M, Jensen KE, Podenphant J, Hansen TM, Skjodt H, Hyldstrup L; TIRA Group. Bone loss in unclassified polyarthritis and early rheumatoid arthritis is better detected by digital x ray radiogrammetry than dual x ray absorptiometry: relationship with disease activity and radiographic outcome. *Ann Rheum Dis.* 2004 Jan;63(1):15-22.

(13) Brower AC. Use of the radiograph to measure the course of rheumatoid arthritis. The gold standard versus fool's gold. *Arthritis Rheum* 1990;33:316–24

(14) Green MJ, Deodhar AA. Bone changes in early rheumatoid arthritis.

Best Pract Res Clin Rheumatol. 2001 Mar;15(1):105-23

(15) Blake GM, Fogelman I. Technical principles of dual energy x-ray absorptiometry. *Semin Nucl Med* 1997;27:210-28

(16) Cann CE. Quantitative CT for determination of bone mineral density: A review. *Radiology* 1988;166:509-22

(17) J. T. Jœrgensen, P. B. Andersen, A. Rosholm and N. Hannover Bjarnason: Digital X-ray radiogrammetry: a new appendicular bone densitometric method with high precision *Clin Physiol.* 2000 Sep;20(5):330-5.

(18) Njeh CF, Fuerst T, Diessel E, Genant HK. Is quantitative ultrasound dependent on bone structure? A reflection. *Osteoporos Int* 2001;12:1-15

(19) Hyldstrup L, Nielsen SP. Metacarpal index by digital X-ray radiogrammetry: normative reference values and comparison with dual X-ray absorptiometry. *J Clin Densitom.* 2001 Winter;4(4):299-306.

(20) Ward KA, Cotton J, Adams JE. A technical and clinical evaluation of digital X-ray radiogrammetry. *Osteoporos Int.* 2003 Jun;14(5):389-95.

(21) Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol* 1977;18:481–91.

(22) Haugeberg G, Lodder MC, Lems WF, Uhlig T, ORstavik RE, Dijkmans BA, Kvien TK, Woolf AD.Hand cortical bone mass and its associations with radiographic joint damage and fractures in 50-70 year old female patients with rheumatoid arthritis: cross sectional Oslo-Truro-Amsterdam (OSTRA) collaborative study. *Ann Rheum Dis.* 2004 Oct;63(10):1331-4.

(23) Böttcher J, Malich A, Pfeil A, Petrovitch A, Lehmann G, Heyne JP, Hein G, Kaiser WA.Potential clinical relevance of digital radiogrammetry for quantification of periarticular bone demineralization in patients suffering from rheumatoid arthritis depending on severity and compared with DXA. *Eur Radiol.* 2004 Apr;14(4):631-7

(24) Stewart A, Mackenzie LM, Black AJ, Reid DM..Predicting erosive disease in rheumatoid arthritis. A longitudinal study of changes in bone density using digital X-ray radiogrammetry: a pilot study. *Rheumatology (Oxford).* 2004 Aug 24 (Epub ahead of print)

(25) Bouxsein ML, Palermo L, Yeung C, Black DM. Digital X-ray radiogrammetry predicts hip, wrist and vertebral fracture risk in elderly women:
a prospective analysis from the study of osteoporotic fractures. *Osteoporos Int.* 2002 May;13(5):358-65.

(26) Bonnick SL, Johnston CC Jr, Kleerekoper M, Lindsay R, Miller P, Sherwood L, Siris E. Importance of precision in bone density measurements.
J Clin Densitom. 2001 Summer;4(2):105-10.

(27) KANIS J. A. (1996) Assessment of bone mass. In: *Textbook of Osteoporosis.* (ed Kanis, J. A.), pp. 71-105. Blackwell Science Ltd, Oxford.

(28) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10

(29) M C Lodder, W F Lems, H J Ader, A E Marthinsen, S C C M van Coeverden, P Lips, J C Netelenbos, B A C Dijkmans and J C Roos. Reproducibility of bone mineral density measurement in daily practice. *Annals of the Rheumatic Diseases* 2004;63:285-289

(30) Ravaud P, Reny JL, Giraudeau B, Porcher R, Dougados M, Roux C. Individual smallest detectable difference in bone mineral density measurements. *J Bone Miner Res.* 1999 Aug;14(8):1449-56.

(31) Barnett E, Nordin B. The radiological diagnosis of osteoporosis: a new approach. *Clinical Radiology* 11, 166-174. 1960.

(32) THODBERG H. H., JENSEN J. K. & ROSHOLM A. (1999) BMD from digital X-ray radiogrammetry: sensitivity to details of the image capture (Abstract). *J Bone Miner Res*, 14 (Suppl.), S369S369.

(33) Rosholm A, Hyldstrup L, Baeksgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital x-ray radiogrammetry: Theoretical background and clinical testing. *Osteoporos.Int.* 12, 961-969. 2001.

(34) Baadegaard N, Linde R, Wendt O, Rosholm A (2001) Digital X-ray radiogrammetry on hand X-rays. Pronosco A/S, Vaedbaek, Denmark

(35) BLACK D. M., PALERMO L., WALLACE R., HARRIS E. & CUMMINGS S. R. (1999) Assessment of BMD at the forearm by digital X-ray radiogrammetry: normative reference data. (Abstract). *J Bone Miner Res*, 14 (Suppl.), S252S252.

(36) Pronosco X-posure System TM.User manual. English version 2 . Pronosco. Sectra Pronosco A/S, Herlev, Denmark

(37) Morton S.J, Dual Energy X-Ray. Absorptiometry (DXA) in early Rheumatoid arthritis. An investigation of novel DXA Regions of interest in the hand. Division of clinical Sciences, School of medicine. University of Leeds. Project submitted for the degree of Bachelor of science in clinical sciences 2002.

(38) The WHO Study Group, Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. , The WHO Study Group, World Health Organisation, Geneva (1994).

(39) Blake GM, Wahner HW, Fogelman I 1999 Assessment of Instrument Performance; Precision, Installation of New Equipment and Radiation Dose. In: Blake GM, Wahner HW,

Fogelman I (ed) The evaluation of osteoporosis: Dual Energy X-Ray Absorptiometry and Ultrasound in Clinical Practice. Martin Dunitz, London, pp 147-172

(40) Genant HK, Block JE, Steiger P, Gluer CC, Ettinger B, Harris ST 1989 Appropriate use of bone densitometry. *Radiology* 170:817-822.

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9.0 Appendix

9.1 The results from this study have been presented as two posters at the Annual European Congress of Rheumatology, EULAR, Berlin, June 2004.

9.1.1 **Short-term in-vivo precision for assessment of hand bone density with Dual Energy X-ray Absorptiometrty (DXA) and Digital X-ray Radiogrammetry(DXR).**

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BACKGROUND
Quantitative bone measures have been proposed as a new outcome measure and a prognostic indicator of future disease course in RA (ref 1). Dual energy X-ray absorptiometry (DXA) is considered as the gold standard among quantitative bone measures. Digital X-ray radiogrammetry (DXR) is a new promising method for assessment of cortical hand bone mass assessed on conventional hand radiographs. The precision of any method is crucial for assessment of differences between groups and for changes over time on both a group level but particularly of importance on the individual level.

OBJECTIVE
To compare in-vivo short term reproducibility for hand bone density measured by dual energy X-ray absorptiometry (DXA) and digital X-ray radiogrammetry (DXR) in healthy individuals.

METHODS
In-vivo short-term precision for DXA was calculated from duplicate hand measures with repositioning of the hand in between each measure.
In-vivo short-term precision for DXR was calculated from measurements on duplicate hand radiographs performed with repositioning of the hand in between each X-ray.
For each device the precision error was calculated separately for the dominant, non-dominant hand and for mean values of both hands separately.

Equipment tested for in-vivo precision of hand BMD measurement:

DXA (measuring whole hand), Lunar Expert.

DXR, Pronosco X-posure SystemTM, version 2.0. A computerized version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin in 1960, measuring cortical thickness at the 2nd, 3rd and 4th metacarpal bone on hand X-rays.

Statistical methods for calculating measurement error for hand BMD:

- Smallest detectable difference (SDD) with 95% detection limits (SDD, according to Bland and Altman) (ref 2)
- Coefficient of variation (CV) expressed as percentage which is the percentage ratio of the standard deviation (SD) corrected for the mean of paired measurements. CV% = {√ (∑D2 / 2N) / mean} * 100 (N = number of paired observations D = the difference between the two measurements for each subject. Mean = Mean of all BMD measurements) (ref 3).
- Percentage SDD based on the formula: 2*rot2*CV%. (ref 4)

RESULTS

28 healthy subjects (mean (SD) age 29.8 yrs (8.3), BMI 23.4 kg/m2 (1.9), males 17 (60.7%)) were examined.

Mean (SD) BMD kg/m2 for both hands was 0.450 (0.054) for DXA and 0.612 (0.067) for DXR.

Long-term spine phantom CV was 0.80% for DXA and long-term CV based on daily measurements of one hand radiograph was 0.25% for DXR.

Table 1. Reproducibility of Digital X-ray Radiogrammetry (DXR) and Dual Energy X-ray Absorptiometry (DXA) hand BMD measurements.

	DXR-hand BMD		
	Non-dominant hand	Dominant hand	Mean both hands
Bland and Altman's methods			
Mean $_{difference}$ (95% CI)	-0.0005	0.0003	-0.0001
(systematic bias)	(-0.0019, 0.0008)	(-0.0010, 0.0017)	(-0.00115, 0.0008)
SD $_{difference}$	0.0035	0.0034	0.0025
(random measurement error)			
SDD ~95% limits of agreement	±0.0069	±0.0067	±0.0048
(assuming no systematic bias)			
CV (%)	0.41%	0.38%	0.28%
2√2CV (%)	1.16%	1.07%	0.79%

	DEXA-hand BMD		
	Non-dominant hand	Dominant hand	Mean both hands
Bland and Altman's methods			
Mean difference (95% CI)	-0.0016	0.0006	-0.0005
(systematic bias)	(-0.0044, 0.0011)	(-0.0029, 0.0040)	(-0.0025, 0.0014)
SD difference	0.0070	0.0088	0.0050
(random measurement error)			
SDD ~95% limits of agreement	±0.0137	±0.0173	±0.0098
(assuming no systematic bias)			
CV (%)	1.13%	1.33%	0.76%
2√2CV (%)	3.20%	3.76%	2.15%

Mean difference: mean of the difference between the first and the second hand BMD measurement

SD difference: SD of the difference between the first and the second hand BMD measurement

SDD: smallest detectable difference (g/cm2)

CV: coefficient of variation

CONCLUSION

Our findings suggest both methods to have good short-term in-vivo precision measuring hand bone density, however DXR being superior. To improve precision mean values of both hands should be used. Whether DXR is more sensitive than DXA to identify patients with bone loss will also depend on magnitude of bone loss at the measurement site, assessed by the two devices in a studied population. Thus, theoretically a higher rate of bone loss assessed with DXA than DXR in a studied population could compensate for the poorer precision. Further studies are needed to examine hand bone loss in different populations.

References

(1) Green MJ, Deodhar AA. Best Pract Res Clin Rheumatol 2001;15:105-23.

(2) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.

(3) Blake GM, Wahner HW, Fogelman I 1999 Assessment of Instrument Performance; Precision, Installation of New Equipment and Radiation Dose. In: Blake GM, Wahner HW, Fogelman I (ed) The evaluation of osteoporosis: Dual Energy X-Ray Absorptiometry and Ultrasound in Clinical Practice. Martin Dunitz, London, pp 147-172.

(4) Genant HK, Block JE, Steiger P, Gluer CC, Ettinger B, Harris ST 1989 Appropriate use of bone densitometry. Radiology 170:817-822.

9.1.2

Short-term in-vivo precision for assessment of hand bone mass with Digital X-ray Radiogrammetry (DXR) in healthy individuals and rheumatoid arthritis patients.

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BACKGROUND

Hand bone mass has been shown to be associated with fractures both in primary (ref 1) and secondary osteoporosis e.g. rheumatoid arthritis (RA) (ref 2). Further, hand bone mass is a potential outcome marker in RA associated with disease activity (ref 3), physical function (ref 4) and bone damage (ref 2). Digital X-ray radiogrammetry (DXR) is a new promising method for assessment of cortical hand bone mass. The precision of any method is crucial for assessment of differences between groups and for changes over time on both a group level but particularly of importance on the individual level.

OBJECTIVE

To assess hand BMD in-vivo short term reproducibility for DXR in healthy individuals and in patients with RA with various disease severity and disease duration.

MATERIAL & METHODS

Study population:

Group-I: 28 healthy individuals

Group-II: 39 RA patients with various disease severities ranging from mild to disabling disease recruited from a rheumatology department in a County hospital.

Methods:

In-vivo short-term precision for DXR was calculated from measurements on duplicate hand radiographs performed with repositioning of the hand in between each X-ray.

The precision error was calculated for the dominant hand and for mean values of both hands separately.

DXR, Pronosco X-posure SystemTM, version 2.0. A computerized version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin in 1960, measuring cortical thickness at the 2nd, 3rd and 4th metacarpal bone on hand X-rays.

Statistical methods for calculating measurement error for hand BMD:

- Smallest detectable difference (SDD) with 95% detection limits (SDD, according to Bland and Altman) (ref 2)
- Coefficient of variation (CV) expressed as percentage which is the percentage ratio of the standard deviation (SD) corrected for the mean of paired measurements. CV% = {√ (∑D2 / 2N) / mean} * 100 (N = number of paired observations D = the difference between the two measurements for each subject. Mean = Mean of all BMD measurements) (ref 3).
- Percentage SDD based on the formula: 2*rot2*CV%. (ref 4)

RESULTS

Group-I: mean (SD) age 29.8 yrs (8.3), BMI 23.4 kg/m2 (1.9), males 17 (60.7%).
Group-II: mean (SD) age was 55.8 (11.9) years, body weight 69.4 (13.4) kg and 79.5% were females. Mean grip strength was 29.8 (22.6) for left hand and 28.6 (19.0) for right hand (kPa) and disease duration was 16.0 (12.6) years.

Long-term CV based on daily measurements of one hand radiograph was 0.25% for DXR.

Table 1. Reproducibility of Digital X-ray Radiogrammetry (DXR) hand BMD measurements in 28 healthy subjects and 39 rheumatoid arthritis patients.

	DXR-hand BMD – healthy individuals	
	Dominant hand	**Mean both hands**
Mean (SD) DXR BMD (g/cm^2)	0.623 (0.070)	0.612 (0.067)
Bland and Altman's methods		
Mean $_{difference}$ (95% CI) (systematic bias)	0.0003 (-0.0010, 0.0017)	-0.0001 (-0.00115, 0.0008)
SD $_{difference}$ (random measurement error)	0.0034	0.0025
SDD ~95% limits of agreement (assuming no systematic bias)	±0.0067	±0.0048
CV (%)	0.38%	0.28%
2√2CV (%)	1.07%	0.79%

	DXR-hand BMD – RA patients	
	Dominant hand	**Mean both hands**
Mean (SD) DXR BMD (g/cm^2)	0.513 (0.108)	0.510 (0.108)
Bland and Altman's methods		
Mean $_{difference}$ (95% CI) (systematic bias)	0.0008 (-0.0010, 0,0026)	0.0000 (-0.0010, 0.0010)
SD $_{difference}$ (random measurement error)	0.0057	0.0033
SDD ~95% limits of agreement (assuming no systematic bias)	± 0.0111	±0.0065
CV (%)	0.61%	0.46%
2√2CV (%)	2.21%	1.30%

Mean difference: mean of the difference between the first and the second hand BMD measurement
SD difference: SD of the difference between the first and the second hand BMD measurement
SDD: smallest detectable difference (g/cm2)
CV: coefficient of variation

CONCLUSION

Our findings shows that the DXR method measuring cortical hand bone mass has superior short-term in-vivo precision and is capable to detect even small changes in hand cortical bone mass. Our data also demonstrate that mean values of both hands should be used to achieve the best precision and that precision is dependent on the BMD level of the examined individuals.

References

(1) Bouxsein ML et al. Osteoporos Int 2002;13:358-65.
(2) Haugeberg G et al. Ann.Rheum Dis. 2004 Accepted for publication.
(3) Deodhar AA et al. Arthritis Rheum 1995;38:1204-10.
(4) Deodhar AA et al. Ann Rheum Dis 2003;62:767-70.